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Nitrous oxide for pneumoperitoneum: No laughing matter this! A prospective single blind case controlled study

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ABSTRACT

Background: The search for the perfect insufflating gas has been elusive. Even though Carbon dioxide (CO_2) is the most commonly used gas, it has numerous cardiovascular, respiratory and hemodynamic side effects, which have often been taken for granted. In the current scenario of ever expanding and complex indications for Laparoscopic Surgery these changes have an increasing implication of placing the patient at risk. Nitrous Oxide (N_2O) has now made a comeback and shown by recent studies to be as safe as CO_2 for creating pneumoperitoneum (PP). The purpose of our study is to determine whether benefits of N_2O (PP) outweigh those of CO_2 PP in Laparoscopic Surgery.

Material and methods: All patients undergoing Laparoscopic Surgery over an 8 week period were divided into two groups. Data were collected prospectively for Group I {$N_2O(n = 38)$} and Group II {CO_2 PP ($n = 39$)}. Heart rate, Mean Arterial Blood Pressure, End-Tidal CO_2, Arterial pH, Peak Airway Pressure, Minute Ventilation and O_2 Saturation were recorded before PP, 15 minutes after PP and 10 minutes after exsufflation. Intraoperative anesthetic agent and postoperative pain medication use was recorded. Pain was assessed by means of visual analog scale (VAS) at postoperative hours 2 and 4 and on day1. Results tabulated and analyzed statistically.

Results: There was no statistical difference in age, sex, weight, complexity of surgery (type of procedure and duration of PP), Anesthetic risk, and duration of hospitalization between the two groups. Mean End-Tidal CO_2 increase was greater despite a greater mean intraoperative increase in Minute Ventilation in group II, Heart Rate, Arterial pH, Mean Arterial Pressure under anesthesia were significantly higher in group II. The quantum of intraoperative anesthetic agent and postoperative pain (as assessed by Visual Analog Scale) was less in group I.

Conclusion: This is an initial study assessing the use of N_2O for insufflation; the results of our study suggest N_2O PP has a definitive advantage over CO_2 PP. Further multicentric randomized trials are necessary before N_2O becomes the standard insufflating agent.

1. Introduction

Carbon dioxide (CO_2) is presently the universally used agent for creating a pneumoperitoneum (PP). It is inexpensive, highly soluble in blood, rapidly eliminated, and suppresses combustion.[1,2] It does, however, possess metabolic, hemodynamic, and cardiovascular adverse effects such as hypercarbia, acidosis, peritoneal irritation and cardiac arrhythmias.[3–6] These complex physiological adjustments associated with CO_2 PP are often ignored in Laparoscopic surgery. Although these conditions may be tolerated in healthy individuals, the elderly and patients with preexisting medical conditions may be placed at greater peril.[3–8]

Prior to the use of CO_2, N_2O was the preferred gas for PP.[9–12] N_2O shares several advantages with CO_2. It is also inexpensive, readily absorbed, and rapidly eliminated from the body. It also has anesthetic and analgesic properties, without the hemodynamic side effects of CO_2.[8,13–15] Even though it does not support combustion it does not suppress combustion.[13] This theoretical fear of combustion, a misunderstanding of the physical chemistry of nitrous oxide, and two anecdotal case reports of intraperitoneal explosions during female sterilization procedures led to a rapid decline in its use in laparoscopy.[16,17] N_2O has now made a comeback and shown by recent clinical and experimental studies to be as safe as CO_2 for creating PP.[10–13,18–20]

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With this ever increasing body of evidence stacking in favor of N_2O, we decided to reconsider and evaluate the efficacy of N_2O as an agent for PP. The aim of this prospective, single blind, clinical trial was to determine whether benefits of N_2O PP outweigh those of CO_2 PP in Laparoscopic Surgery.

2. Material and methods

Following an approval from the ethics committee and an informed consent from the patients, all patients over the age of 21 who were undergoing laparoscopic surgery at our hospital were offered the opportunity to participate in this trial. Over an 8 week period from March to May 2009, Seventy seven consecutive patients who presented to the hospital were divided into two groups Group I {N_2O ($n = 38$)} and Group II {CO_2 ($n = 39$)}.

The Anesthesiologists were blinded to the PP gas used. Patients were premedicated with Lorazepam 2 mg orally 6 h before surgery. Intravenous Inj. Glycopyrrolate 0.2 mg was administered at the time of induction. Anesthesia was induced with 2 mg/kg Propofol with 2 ml of 2% plain lignocaine (without preservative) in the same syringe, 4 µg/kg Inj. Fentanyl and 0.5 mg/kg Atracurium (muscle relaxant) were also given for intubation and 10 mg of Atracurium was repeated at 30 min intervals. Patient was ventilated with bag and mask for 3 min and intubated with a suitably sized endotracheal tube. Anesthesia was maintained with Isoflurane 1% in an oxygen/air mixture (inspired oxygen concentration 50%). Enough isoflurane was delivered for the patient to tolerate the surgery, the efficacy being assessed by the blood pressure, heart rate and possible movements of the patient. If the patient showed signs of too light anesthesia, the inspiratory isoflurane concentration was increased with increments of 0.5 vol%. The patients were ventilated in a respirator, ventilation being adjusted to normoventilation by capnometry. At the end of the procedure, the muscle relaxation was reversed with 2.5 mg Neostigmine combined with 0.5 mg Glycopyrrolate.

Heart rate, Blood pressure from the radial artery, pulse oximetry, and capnometry (end expiratory [ET] CO_2 concentration) were monitored continuously during the operation (Aestiva 5, Datex-Ohmeda, India). Arterial blood samples were obtained during the procedure to analyze blood pH, PO_2, and $PaCO_2$. The end expiratory gas isoflurane concentration was recorded by an anesthetic gas meter (S-5 Datex-Ohmeda, India). The isoflurane consumption to maintain the lowest possible anesthesia level was calculated as minimal alveolar concentration (MAC)-hours{MAC-h}, recording the isoflurane concentrations which the patient needed; 1.15% was used as the isoflurane MAC value.[21] Baseline values of the above parameters before commencement of operation, follow-up values at 15 min after commencing PP and just before exsufflation were recorded.

During the procedure, intra-abdominal pressure was maintained automatically at 12–14 mm Hg by an insufflator (Karl Storz Endoscopy India Private Ltd). Monopolar electrosurgery and/or ultrasonic dissection (harmonic scalpel) were used in all operations.

After the operation, patients received an initial bolus of 100 mg Tramadol intramuscularly, with subsequent doses of 50 mg 4–6th hourly (upto a maximum total dose of 400 mg) depending on discretion of the nurse or the request of the patient. Intravenous Diclofenac (1 mg/kg) was also used at the judgment of the nurse. Once Oral feeds were started, patients were switched to oral analgesics tablets (37.5 mg Tramadol + 375 mg Acetaminophen). Total analgesic consumption was recorded. The intensity of postoperative pain was assessed by the patients themselves using a visual analog scale for pain scoring (on a 0–10 scale) at postoperative hours 2, 4 and 24.

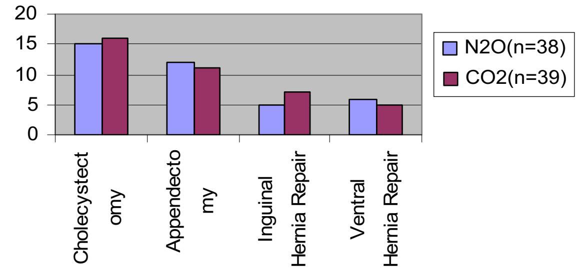
For statistical analysis, the Student's *t*-test, chi-square test, and the Mann–Whitney *U* test for nonparametric data were performed. A *p* value <0.05 was considered to represent a statistically significant difference between groups.

3. Results

In our study there were a total of 77 patients. 38 in the N_2O group 39 in the group which received CO_2 for PP. The two groups were well matched with respect to demographic information (age, sex, and weight), complexity of surgery (type of procedure and duration of PP), Anesthetic risk, and duration of hospitalization.

Distribution of laparoscopic procedures.

Procedure	N_2O ($n = 38$)	CO_2 ($n = 39$)
Cholecystectomy	15	16
Appendectomy	12	11
Inguinal hernia repair	5	7
Ventral hernia repair	6	5



Pre and perioperative characteristics of the study population.

Variable	$N_2O(n = 38)$	$CO_2(n = 39)$	*p* Value
Age (years, range)	47(25–69)	48(28–68)	NS
Sex (male/female)	20/18	22/17	NS
Weight (Kg)	67.6 ± 14.5	68.7 ± 10.0	NS
Duration of pneumoperitoneum (min)	52.1 ± 22	51.9 ± 23.7	NS
Anesthetic risk (ASA > 2)	4(10.5%)	4(10.2%)	NS
Duration of hospitalization (days)	1.6 ± 0.6	1.7 ± 0.7	NS

There was a significant difference between N_2O and CO_2 groups in the intraoperative heart rate changes, mean arterial pressure (MAP) changes during PP, the CO_2 group showing a substantial rise in heart rate and MAP as compared to the N_2O group.

Changes in heart rate and mean arterial pressure (MAP) during N_2O and CO_2 insufflation (difference in mean values before and during PP).

Parameters	$N_2O(n = 38)$	$CO_2(n = 39)$	*p* Value
ΔHeart rate (beats/min)	3 ± 6.7	8.4 ± 9.1	$p < 0.01$
ΔMean arterial pressure (mmHg)	5.0 ± 10.8	12.1 ± 11.8	$p < 0.01$

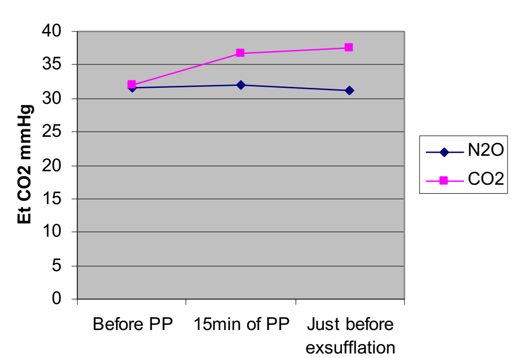
Arterial pH during N_2O and CO_2 insufflation.

pH	N_2O	CO_2	*p* Value
Before PP	7.44 ± 0.04	7.43 ± 0.05	NS
15 min of PP	7.41 ± 0.03	7.38 ± 0.03	$p < 0.01$
Just before exsufflation	7.40 ± 0.04	7.36 ± 0.04	$p < 0.01$

During CO_2 insufflation, there was significant respiratory acidosis, as assessed by means of $ETCO_2$ and pH monitoring during the procedure. In the group receiving CO_2 for PP, there was a significant increase in $ETCO_2$ concentrations despite a concurrent increase in the minute ventilation. There was a substantial fall in the arterial pH for the patients in CO_2 group. These phenomena were not observed in the N_2O group.

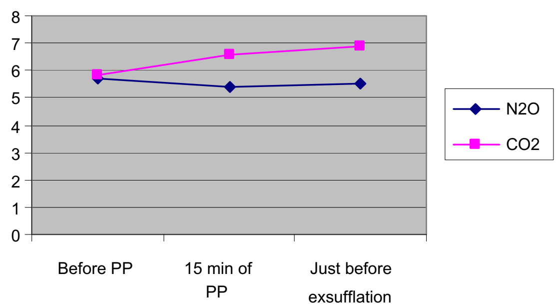
Mean end tidal CO_2 (mmHg) values during N_2O and CO_2 insufflation.

Mean EtCO2	N_2O	CO_2	*p* Value
Before PP	31.6	32	NS
15 min of PP	32	36.8	$p < 0.01$
Just before exsufflation	31.2	37.6	$p < 0.01$



Mean minute ventilation (L/min) values during N_2O and CO_2 insufflation.

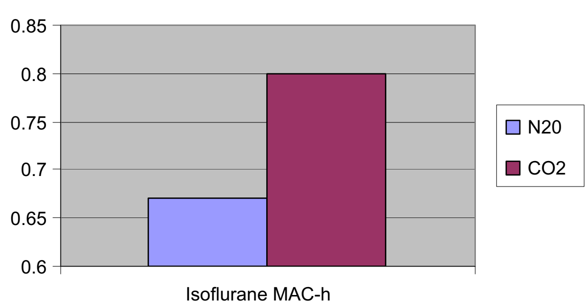
Mean minute ventilation	N_2O	CO_2	*p* Value
Before PP	5.7	5.8	NS
15 min of PP	5.4	6.6	$p < 0.01$
Just before exsufflation	5.5	6.9	$p < 0.01$



The total amount of anesthetic (isoflurane) required for the procedure was significantly lower in the N_2O (0.67 MAC-h) than in the CO_2 group (0.8 MAC-h).

Total amount of anesthetic (MAC-h) needed in the N_2O and CO_2 groups.

	N_2O	CO_2	*p* Value
Isoflurane MAC-h	0.67	0.8	$p < 0.05$



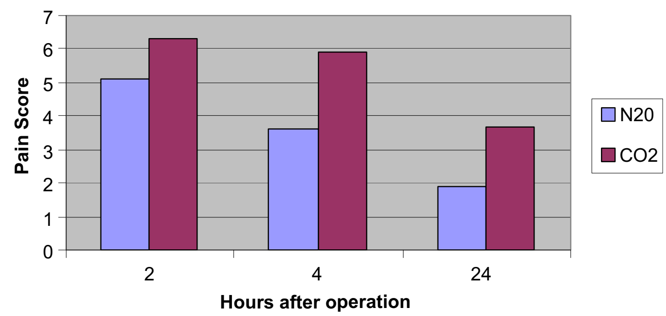
The total analgesic consumption was lower in the N_2O group but this difference was not statistically significant. Despite receiving a similar quantum of pain relief, the patients in the N_2O group had significantly less pain than patients in the CO_2 group at 2 h, 4 h and 24 h postoperatively.

Postoperative analgesic medication (mg) needed in the N_2O and CO_2 groups.

Analgesic	N_2O	CO_2	*p* Value
Tramadol (IM + oral)	146.2 ± 26.8	158.2 ± 37.4	NS
Diclofenac (IV)	102.4 ± 10.9	110.6 ± 10.4	NS
Acetaminophen (oral)	578 ± 110	624 ± 127	NS

Visual analogue pain scores in patients in hours at 2, 4 and 24 h of N_2O PP and CO_2 PP.

Hours	N_2O	CO_2	*p* Value
2	5.1	6.3	$p < 0.05$
4	3.6	5.9	$p < 0.01$
24	1.9	3.7	$p < 0.01$



4. Discussion

This is an initial study assessing the use of N_2O for insufflation; the results of our study suggest N_2O PP has a definitive advantage over CO_2 PP.

Patients who received N_2O for insufflation had lower pain scores on the visual analog scale, this was despite the consumption of analgesics being similar in both groups, or even tended to be lower in the N_2O group. These results are in accordance with those of previous studies.[8,14,15,22] Two studies assessed pain associated with diagnostic laparoscopy under local anesthesia.[8,22] Both studies were randomized and double blind, both studies demonstrated less postoperative discomfort with N_2O than with CO_2. However, in these studies, patients underwent only diagnostic laparoscopy under local anesthesia; the patient groups were heterogeneous with regard to their basic illnesses and in one of the studies pain was assessed by arbitrary scoring.[22] Aitola et al. in their prospective randomized study of 40 patients compared N_2O and CO_2 PP during laparoscopic cholecystectomy.[15] They showed that N_2O PP produced less postoperative pain and required a decreased quantity of anesthetic for the surgical procedure than did CO_2 PP. More recently, Tsereteli et al. in their prospective randomized clinical trial comparing N_2O and CO_2 PP during upper gastrointestinal laparoscopic surgery have shown that postoperative pain is less with N_2O PP than with CO_2 PP.[14]

The mechanism underlying the favorable analgesic effect of N_2O is not exactly known. There are several postulates. Phillips et al. suggested that the improved tolerance to N_2O must be due to local effects, because they found no significant levels of absorbed and expired N_2O during or after the procedure.[23] CO_2 may transform into carbonic acid by combining with fluid in the peritoneal cavity, which in turn acts a peritoneal irritant.[24]

In our study we were able to show a reduced amount of anesthetic was needed for patients in the N_2O group. This is in concurrence with other studies.[14,15] The reason behind this phenomenon could be due to the lack of local irritation by N_2O and a favorable effect on the central nervous system (CNS), which would then result in an advantageous interaction with an anesthetic. A higher anesthetic requirement in the CO_2 group might be due to the increased sympathetic activity due to respiratory acidosis, which in turn necessitates an increased administration of anesthetic to keep the patient hemodynamically stable.[25–27]

Even though CO_2 is the most commonly used gas, it has numerous cardiovascular, respiratory and hemodynamic side effects. Complications include hypercarbia, acidosis, tachycardia, decreased stroke volume; arrhythmias, hyperventilation-induced barotrauma, oliguria, increased intracranial pressure, and peritoneal irritability. These have often been taken for granted. In the current scenario of ever expanding and complex indications for Laparoscopic Surgery these changes have an increasing implication of placing the older and less healthy patient at risk.[4–8,13,14]

The main concern arising from the use of CO_2 as pneumoperitoneum gas has been the development of hypercarbia and respiratory acidosis.[6,7] In patients with a normal physiological profile, this can be compensated for by increasing ventilation, but in patients with cardio-respiratory compromise, compensation is not always possible. In such cases, conversion from CO_2 to N_2O has been found useful.[13,26] Hunter et al. in a large animal study demonstrated that end-tidal CO_2 measurement may significantly underestimate arterial pCO_2, and this difference is magnified when a rapid ventilatory rate is required to compensate for respiratory acidosis. The same study suggested that fetal acidosis developed in pregnant ewe model receiving CO_2 pneumoperitoneum.[20] A study by Gardner et al. recommends nitrous oxide as the primary insufflation gas in patients with respiratory compromise.[26]

The main theoretic concern related to the use of N_2O is its inability to suppress combustion. N_2O is not combustible, but in the presence of a volatile gas, such as hydrogen or methane, N_2O is an oxidizer with properties similar to room air.[11–13]

N_2O was the preferred gas for pneumoperitoneum in the 1970s–80s. This was until it received ignominy based on two unsubstantiated case reports, one from Sri Lanka and the other from Egypt.[16,17] In both cases, combustion apparently occurred after all electrical current had ceased. So it is unlikely that these cases represent N_2O induced/supported ignition. But it is unlikely that we will know what really happened in those two scenarios and it seems most unreasonable to implicate N_2O.

An increasing body of literature (physical chemistry and medical), have demonstrated the safety of N_2O.[10–13,18–20] Several studies have demonstrated that even without bowel preparation, methane and hydrogen were undetectable in the pneumoperitoneum of patients undergoing laparoscopic cholecystectomy.[11–13,27] It is theoretically possible for an accidental electrosurgical colonic perforation in a methane- or hydrogen-filled colon to ignite in N_2O PP.[12] Hydrogen and methane are produced only in the colon by the normal bacterial flora. Assuming the highest reported incidence of accidental colon injury (1 in 2000) and the requirements for large concentrations of hydrogen and methane to cause combustion, it is no surprise that many hundreds of laparoscopic gynecological procedures have been performed in an N_2O environment with electrosurgery without a single episode of combustion.[29–31]

In early colonoscopic polypectomy cases, due to the fear of combustion the colon was insufflated with CO_2. This fear of combustion was found to be theoretical and CO_2 was abandoned in favor of air to simplify insufflation. In a similar vein it seems unreasonable to condemn N_2O PP.

A second potential disadvantage of N_2O is bowel distention, usually observed when N_2O is used as an anesthetic agent. Because N_2O absorbed in the circulation is rapidly eliminated by the lungs, this appears more to be a theoretical question than a practical problem.[28]

The cost of a cylinder of N_2O is no different from the cost of a CO_2 cylinder. In our operating theatre we have a ceiling tower for centralized supply of N_2O and CO_2 and it is just a question of toggling a switch to make the change. In some cases a special connecting cord may be required. This cord is inexpensive and N_2O cylinders are ubiquitous in operating suites, but one needs to check with the insufflator manufacturer because some may need to be adjusted for N_2O.

In conclusion, the use of N_2O as the gas for PP is safe and has several advantages over CO_2, including less postoperative pain, decreased risk of hemodynamic and cardiovascular side effects as discussed previously and hence it provides a safe alternative gas for abdominal insufflation in laparoscopic operations.

Conflict of interest

The authors have no conflicts of interest or financial ties to disclose.

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None to declare.

Ethical approval

Ethical Approval for the work has been obtained from the ethical committee at Apollo Hospitals, Chennai (institution in which study was performed) and subjects gave informed consent to the work.

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